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Nutrition and Renal Disease II

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Nutrition and Renal Disease II

ROBERT W. WINTERS, M.D.*

ACUTE RENAL FAILURE†

Under this heading is included a wide variety of conditions, the common feature of which is the production of an acute and extensive destruction of the renal tubular epithelium. Etiologically, acute renal failure may be produced by marked or prolonged reductions in renal blood flow (hemorrhage, severe dehydration), by a variety of nephrotoxins (*e.g.,* mercury, carbon tetrachloride), by intravascular hemolysis (mismatched blood transfusion, inadvertant infusion of distilled water) or by severe injuries (such as the "crush syndrome") where a combination of the above factors is involved.

Clinically, the disorder may be mild or severe. There are two distinct phases to the fully developed disorder. The first is the oliguric phase, where urine volume is scant (50 to 150 ml/d). Decrease in urine flow usually develops within a few hours after the original insult and becomes marked within a day or two. The duration of this phase is generally about a week to 10 days but may be as long as 20 days. The oliguric phase is usually rather abruptly terminated by a rapid and progressive increase in daily urine volume, which within a few days reaches values of 3 to 7 liters (the polyuric phase). The duration of polyuria is quite variable. Most often, the urine volume gradually approaches more normal values as the polyuric phase blends into a convalescent phase.

Pathophysiology (19, 27)

The disturbances occurring in renal function in acute renal failure will be discussed in terms of the two major phases of the disorder.

Oliguric Phase: During the oliguric phase, urine volume is quite small; complete cessation of urine formation is very rare, however, except in cases where there is complete obstruction of the lower tract. A reduction in GFR is almost certainly a contributing factor to the oliguria, but there are other factors of even greater importance. Oliver *et al.* (29) in their microdissection studies of the nephrons of acute tubular necrosis have clearly shown that rupture of the basement membranes of the tubules occurs, as well as destruction of the tubular epithelium. The implication of these studies is that the tubular epithelium in this condition can no longer function as a discriminating barrier. Rather, these breaks in the structural integrity of the nephron permit an indiscriminate

*Department of Biochemistry, University of Pennsylvania, School of Medicine, Philadelphia, Pennsylvania.

†Glossary of frequently used terms appears in Part I, preceding issue.

diffusion of glomerular filtrate back into the blood, precluding any selective modification of the filtrate.

In acute renal failure, the effects of this back-diffusion of the bulk of the glomerular filtrate are similar to those of chronic renal failure except for the more acute and more intense nature of the disturbance. NPN rises rapidly in blood, the rate of rise being conditioned by the previous nutritional status of the patient, by the degree of stress being sustained, and by the concurrent caloric intake. Accompanying the azotemia is an accumulation of the acidic products of protein catabolism (phosphate, sulfate) which produce metabolic acidosis. Since potassium is also released into the extracellular fluid as tissue is catabolized, hyperkalemia is a constant threat.

Polyuric Phase: With the onset of the polyuric phase the urine is quite dilute and contains large amounts of sodium, potassium and chloride. Transient aminoaciduria may also occur. There is a marked inability to produce a concentrated urine during fluid restriction in this phase. All of these phenomena represent the combined effects of an osmotic diuresis (see above) plus specific tubular disturbances in the reabsorption. The polyuria gradually subsides as do the other abnormalities. Normal renal function may eventually be achieved in some patients while in others significant abnormalities of function are apparently permanent.

Nutritional Considerations

A. Oliguric Phase

Water: Water balance in the oliguric phase must be managed with great care in order to avoid dehydration on the one hand and edema and hyponatremia on the other.* In order to manage water intake properly one must consider the routes and amounts of water being lost or gained, and from this compute the need as the difference between loss and gain.

Water loss may proceed through four channels: (a) through the skin and lungs as insensible loss, (b) through the urine, (c) through losses of gastrointestinal secretions by either vomiting or diarrhea and (d) through the skin as sweat. The insensible loss is pure water, and the magnitude of this loss bears a direct relationship to caloric expenditure (averaging about 45 ml/100 calories expended). Put in these terms, it is not difficult to visualize the effect that factors which alter metabolic rate (*e.g.,* fever) would have in changing the rate of insensible loss. Ordinarily somewhere between 600 and 800 ml of water per day may be accounted as insensible loss. Losses through the urine during the oliguric phase are of course small, but the urine volume should be measured and

*It is recognized that in many patients, development of acute renal failure may be associated with circumstances in which a considerable deficit of salt and water have been incurred. The replacement of these deficits constitutes an important phase in the early management of such patients. In the discussion here it is assumed that such deficits have been repaired and that the patient begins with good hydration.

added in the balance. Likewise, it is usually possible to measure the amount of water lost from gastrointestinal routes. The losses incurred through sweating must usually be estimated; changes in body weight, if accurately measured, constitute an excellent method of approximating sweat losses.

In considering the water intake for the oliguric patient, one must take account of the water of oxidation as well as the preformed tissue water, both of which are being released to the general body fluids as a result of the catabolism of tissue. Calculations show that with an average metabolic mixture, some 400 to 500 ml of water per day is made available as a result of these processes. Failure to take account of this hidden water leads to serious errors of management. For example, during 10 days of oliguria the error could amount to as much as 5 liters of water!

Accurate daily body weight measurements are an invaluable guide in assessing the state of hydration of the patient with acute renal failure. Appropriate adjustments of water intake should be made using such data. During the oliguric phase, in general, it is best to allow some daily weight loss (usually 0.5 kg) to occur rather than attempt to keep body weight absolutely constant throughout.

Sodium and Chloride: In the absence of large extrarenal losses in the form of gastrointestinal secretions or sweating, little sodium or chloride should be given to the patient with acute renal failure during the phase of oliguria. If such losses do occur, appropriate additions of sodium and chloride should be made to the intake, the exact amounts to be determined either by direct analysis of the loss as in the case of gastrointestinal secretions or by an estimate, in the case of sweating. (It should be remembered that sweat is a hypotonic fluid with respect to sodium and chloride). The sodium given to replace such losses should not be entirely as sodium chloride since in the absence of kidney function this will provide a chloride excess. It is generally perferable to give sodium as two-thirds sodium chloride and one-third sodium bicarbonate.

One of the most difficult problems in the management of acute renal failure is that of hyponatremia. Providing previous deficits of sodium and chloride have been repaired, the occurrence of hyponatremia nearly always signifies that too much water has been given in relation to salt. Mild degrees of hyponatremia (serum sodium reduced to 130 mEq/L) can be managed merely by curtailing subsequent water intake. However, with severe hyponatremia associated with serious symptoms resulting from cellular overhydration (*e.g.*, convulsions) treatment with hypertonic sodium solutions* is indicated. In the absence of such symptoms, serious degrees of hyponatremia are managed preferably by a combination of vigorous restriction of water intake with only partial correction

*The amount of sodium to be given can be accurately calculated from this formula: Na required = (140 — observed serum Na) x 0.6 x Body Wt. in kg. As in the case of repair of sodium deficit, this sodium should be given as a balanced solution—partly as NaCl, partly as $NaHCO_3$—the exact proportions of these two to be decided by the prevailing disturbances of acid-base equilibrium.

with hypertonic sodium solutions. The artificial kidney provides a valuable tool in treatment of hyponatremia of acute renal failure.

Calories: The need for non-protein calories is urgent during the phase of oliguria in order to prevent ketosis and to minimize endogenous catabolism of tissue, thereby reducing the degree of accumulation of phosphate, sulfate and potassium in the serum. The minimum caloric intake necessary to achieve these aims is 100 to 150 gms. (11) of carbohydrate per day as glucose or invert sugar. More is desirable. Providing even this much carbohydrate poses difficult technical problems, since the total amount of fluid available as a vehicle is sharply limited by water requirements (see above) and this necessitates the use of hypertonic fluids. The latter are quite irritating to veins and may lead to thrombosis. This can be minimized by using a plastic catheter inserted in a large vessel. The possibilities of using caloric sources other than carbohydrates for parenteral administration have been suggested. Intravenous fat emulsions are still in the experimental stage. The use of ethyl alcohol (7 Calories per gram) as a caloric source deserves further study.

In some patients the oral route may be used even though the possibility of vomiting is very real; and this in turn may considerably complicate management. Hard candy has been recommended as an additional means of administering carbohydrate calories.

Even under ideal circumstances, exclusive provision of carbohydrate can do no more than provide a fraction of the total caloric expenditure. In order to circumvent this difficulty several investigators (see 28) have advocated force-feeding of a high caloric diet in which the caloric sources are fat, either as butter or a commercial fat emulsion, and sugar.*

Nausea and vomiting are sometimes problems with this mixture, but it is claimed that continuous slow administration by intragastric drip obviates this difficulty. Steamed rice with liberal amounts of butter and sugar may also be used if tolerated.

In all cases, water-soluble vitamins should be added to the daily intravenous fluids.

Potassium: Potassium intoxication represents one of the serious threats to life of the oliguric patient. Careful attention must therefore be paid to the level of serum potassium and to the electrocardiogram. Obviously no exogenous potassium should be given. Provision of adequate calories (see above) tends to minimize the rise of serum potassium by reducing tissue wasting. Yet in some patients even with good management, hyperkalemia occurs. This is particularly frequent in patients who have sustained excessive necrosis of tissue or internal bleeding. With the breakdown of the dead tissue or the extravasated erythrocytes, large

*A typical diet of this type is as follows: sugar, 150 gm; butter, 150 gm; flour and water to the consistency of soup. Flavoring should be added. The mixture is better tolerated if chilled. Commercial oral fat emulsions may be used with sugar in lieu of the above.

amounts of potassium are released into the extracellular fluid. No amount of exogenous calories can affect the rate of these processes.

There are a number of conservative measures which may be successful in the treatment of hyperkalemia (19, 27). Intravenous infusion of calcium gluconate is a valuable immediate antagonist to the effects of hyperkalemia insofar as the electrocardiographic manifestations are concerned. Obviously this measure does not remove any potassium from the body. The use of insulin and glucose, by promoting glycogen deposition, will cause a fall in serum potassium which constitutes another emergency measure. Again the effects are transient and do not attack the cause of the problem.

Carboxylic ion exchange resins have been used as a measure designed to remove potassium from the body (see 30). When introduced into the gastrointestinal tract, either by mouth or by retention enema, these substances take up potassium from the gastrointestinal secretions in exchange for another cation (hydrogen, ammonium or sodium) which is absorbed. The resins themselves being non-absorbable carry the potassium out into the feces. Although their capacity and affinity for potassium are not great, resins have been used effectively in the treatment of hyperkalemia. They are not, however, ideal therapy for the following reasons: (a) they are not consistently effective; (b) by the oral route (which is the most effective) they are quite distasteful and may lead to vomiting; (c) the hydrogen or ammonium cycle resin may aggravate the acidosis; (d) the sodium cycle resin may add more sodium to the body than is desired from a therapeutic point of view.

The best treatment for hyperkalemia is extracorporeal dialysis (artificial kidney), which in experienced hands is reasonably safe and very effective. Peritoneal dialysis also may be effective and requires less elaborate equipment but does carry the risk of intraperitoneal infection. For further details of these methods of treatment, the interested reader is referred to the literature (19, 27).

Acidosis: Ordinary moderate degrees of acidosis are not associated with marked or disturbing symptoms and should not be treated. In fact, in view of the hyperphosphatemia and hypocalcemia which develop, some degree of acidosis is desirable because of its protective effect against the development of overt tetany. With proper caloric intake, serious acidosis can be prevented and specific treatment (*i.e.*, with sodium bicarbonate) is not often necessary. It should be remembered that patients with metabolic acidosis of acute renal failure frequently maintain low values of pCO_2 even when blood pH is brought back to normal (31). The implication of this finding is that abrupt restoration of serum bicarbonate to normal may lead to an alkalosis, which in turn may lead to serious tetany and even death. The dilemma in attempting treatment of the acidosis is as great as that in treating hyponatremia. The composition of the plasma in acute renal failure is such that in the absence of kidney function elevation of the serum bicarbonate concentration can be achieved only by elevation of the concentration of sodium. In turn, this leads to thirst, and frequently the only

result of such therapy is to substitute thirst for what was an asymptomatic acidosis. As in the case of hyperkalemia, the artificial kidney offers a superior method for treatment of acidosis.

B. Polyuric Phase

With the onset of polyuria, the tendency of many physicians is to lower the therapeutic guard. It is not often enough realized that many patients survive the oliguric phase only to die during the polyuric phase of the disease.

Due to the large urine volumes dehydration is now a constant threat. Fluid intake must be rapidly adjusted to the increasing urine volume, in addition to provision of increments to cover extrarenal losses. Salt losses through urine may be considerable and must be replaced promptly in order to prevent serious salt depletion. For most accurate replacement therapy, chemical analysis of the urine for sodium (and potassium) should be carried out daily until the peak of the diuresis is past. Potassium losses may also be extensive and if allowed to continue unreplaced will eventuate in serious potassium depletion.

With the subsiding of the azotemia and the gradual return of renal function, a diet adequate in all respects and high in protein should be offered. Often five meals instead of the usual three are better tolerated until the patient regains appetite and normal gastrointestinal function. The need for vigorous dietary therapy with respect to protein and caloric needs during this late phase of the disorder should be obvious when it is realized that the patient has been subsisting principally upon his own body stores for the previous 20 or more days, frequently in the face of severe trauma, major surgery and/or serious infection. Indeed, measurements of body composition of such patients during the course of acute renal failure show major losses of body fat as well as of lean body mass (19). The services of a skilled dietitian are particularly valuable during this period in meeting all dietary objectives while still respecting the likes and dislikes of the patient.

THE NEPHROTIC SYNDROME

The cardinal features of the nephrotic syndrome are (a) marked edema, (b) profuse proteinuria, (c) marked hypoalbuminemia, and (d) hyperlipemia. Most frequently, the disease appears without apparent cause in young children, although it may occur during the course of chronic renal failure in adults. The nephrotic syndrome may also appear as the result of syphilis, amyloidosis, disseminated lupus erythematosis, or as a complication of diabetes mellitus (Kimmelstiel-Wilson disease). Rare cases are encountered due to bilateral renal venous thrombosis or to a peculiar reaction to bee stings, or to certain drugs.

By far the most important and often the only symptom of the nephrotic syndrome is massive edema involving the subcutaneous tissues as well as the peritoneal cavity (ascites). In many patients, some "nephritic" components may

form a part of the picture — hematuria, hypertension, and some degree of azotemia. In the usual case, the course is long and punctuated by bouts of edema and remission.

The prognosis of the so-called "pure" nephrotic syndrome in children is variable. In general, about half of such patients will succumb either to infection or to chronic renal failure, which the other half recover, usually after a protracted course. Complete recovery in adults is rare, except in those cases following bee sting or the result of a drug reaction.

Pathophysiology

Proteinuria: Patients with the nephrotic syndrome lose large amounts of protein in the urine, often amounting to 30 or more gm. per day in affected adults. The greatest proportion of the urinary protein is albumin which is indistinguishable from normal serum albumin.

Two general hypotheses have been advanced to explain the profuse proteinuria: (a) that it is due to failure of reabsorption of the small amounts of protein normally filtered at the glomerulus or (b) that abnormally large amounts of protein pass the glomerular membrane as the result of an increase in permeability.

In conjunction with the first hypothesis, it should be noted that the concentration of protein in the normal glomerular filtrate (about 30 mg. %) could account for as much as 43 gm. of urinary protein per day if there were no tubular reabsorption and if the GFR were normal (100 ml/min). However, by indirect methods, Chinard *et al.* (32), have clearly shown that the primary cause of proteinuria is an increase in the amount of protein being filtered, thereby indicating that the primary defect is an abnormal permeability of the glomerular membrane.

Hypoalbuminemia: There is little doubt that albuminuria is a major cause of the hypoalbuminemia and the depletion of the plasma protein pool observed in the nephrotic syndrome. Theoretically, there are at least two additional factors which might condition the degree of depletion: (a) the rate of synthesis of new albumin and (b) the rate of catabolism of albumin.

With respect to the rate of synthesis, the consensus is that it is normal if not accelerated (33) as indeed it must be since patients with the nephrotic syndrome can sustain heavy and prolonged losses of protein in the urine without appreciable further reduction in the level of albumin in the plasma.

The rate of catabolism of albumin has also been studied and found to be accelerated (33). In some patients, this accelerated breakdown of albumin contributes in a major way to the degree of protein depletion. The mechanisms responsible for this increased catabolism are obscure; accelerated catabolism of albumin is not a feature of other types of protein depletion.

Edema Formation: The formation of edema ultimately represents the accumulation of excessive amounts of sodium and water in the interstitial space of the body fluid as a result of the renal retention of these substances in the face of

continuing intake. In any edematous state (30), there is a disturbance between the various forces controlling the distribution of fluid across the capillary membrane (Starling equilibrium). According to the latter, movements outward from the capillary are the result of (a) the capillary hydrostatic pressure and (b) the colloid osmotic pressure of the proteins of the interstitial fluid. Outward movement is limited by two additional factors: (c) the colloid osmotic pressure of the plasma proteins, principally albumin, and (d) the resistance of the tissues to distention. Normally, the net balance of all of these forces is such that the small amounts of fluid filtered from the capillary are returned to the circulation by the lymphatics.

In the nephrotic syndrome, because of the hypoalbuminemia, net fluid movement outward is greatly accelerated and the interstitial fluid space is expanded. The immediate consequence of this movement must be a reduction of the plasma volume, but because of the gradual development of edema, frank symptoms of shock do not appear. However, a state of "circulatory insufficiency" may be thought to exist.

The development of "circulatory insufficiency" has two broad consequences with respect to renal function (33). The first of these is a reduction in GFR resulting in an avid reabsorption of sodium and water by the proximal tubule. The second consequence is an increased rate of secretion of aldosterone by the adrenal cortex and of antidiuretic hormone (ADH) by the posterior pituitary gland. Both of these hormones increase the distal tubular reabsorption of sodium and water. As a result of all of these actions, the kidney produces urine of scant volume and very low in sodium, while retaining large amounts of sodium and water in the body.

Glomerular Filtration Rate (35): The GFR in the nephrotic syndrome is quite variable. Adults with a nephrotic component of chronic renal failure nearly always have some reduction in GFR, but in children the GFR may be reduced, normal or even supernormal. In any given patient, wide fluctuations may be encountered, partly connected with formation or mobilization of edema. Patients with a significant "nephritic" component tend to have greater reductions, and those who go on to renal failure have progressive falls of GFR. The reduction in GFR may not be evident in an elevation of blood urea to obviously pathologic levels because of the accompanying protein depletion associated with reduced urea production.

Nutritional Considerations

Protein Intake (36): In designing a diet for the nephrotic patient, it is important to realize that in a metabolic sense, the nephrotic behaves very much like a patient suffering from protein depletion for any other reason. For example, unlike the normal (adult), the nephrotic patient when given a normal or even low intake of protein, shows a positive nitrogen balance. Typically such patients excrete only small amounts of non-protein nitrogenous compounds in the urine,

again resembling the situation in protein depletion. The minimal protein intake which will maintain a positive nitrogen balance is directly related to the degree of existing protein deficits. Hence during repletion, more dietary protein must be provided to achieve equivalent nitrogen retention in the mildly depleted as compared to the severely depleted patient. However, at any given degree of protein deficit, retention is proportional to the intake, at least over the range of about 1.8 to 3.5 gm. per kg. body weight.

For practical purposes, the amount of protein in the diet should be in the upper part of this range and should be accompanied by provision of full non-protein caloric sources in order to achieve maximal retention. Animal protein should make up an appreciable proportion of the total. Use of commercially available protein supplements is often of value particularly in children. Some evidence indicates that nitrogen retention at very high levels of protein intake (exceeding 3.5 gm/kg) is less than at lower levels (37), although the matter is not completely settled.

Even with a sustained positive nitrogen balance, the rise in plasma proteins is often disappointingly slow. This is no reason to abandon the high protein intake. Rather such an observation merely reflects the serious degree of deficit of labile protein stores, of which the plasma proteins are only one part. Another reason often given for not feeding high protein diets is that they may increase the proteinuria, an observation interpreted to mean that the high protein intake exerts a deleterious effect upon the underlying renal disease. An alternate and more reasonable explanation for these findings is that there has been some temporary increase in the level of plasma albumin as a result of the high protein intake; this in turn leads to an increase in proteinuria simply by increasing the filtered load.

Edema: Relief of edema is frequently one of the most urgent therapeutic demands. Two aspects of the problem of nephrotic edema which are directly related to nutritional considerations will be discussed here: (a) sodium restriction and (b) use of adrenal cortical steroids.

The predominant role of dietary sodium in the pathogenesis of edema has been stressed above. There is no doubt that sodium restriction is very desirable and, if strictly carried out, will limit edema formation. A practical problem, however, frequently arises when one attempts to formulate a diet low in sodium but at the same time palatable enough to supply the urgent needs for protein and calories. Often the only practical compromise is to allow somewhat more sodium than is desirable from the point of view of control of edema in order that the patient will eat.

It should be remembered that the prescription of a low-sodium diet for a nephrotic patient increases the risk of acute salt depletion in the event of extrarenal losses. Most often, salt depletion follows the removal of a large ascitic collection by paracentesis. Following paracentesis, peritoneal fluid rapidly reaccumulates, the source of the new fluid being the plasma volume. As a result,

acute circulatory collapse may occur due to the rapid internal sequestration of fluid. Such a complication should be carefully searched for in any patient undergoing paracentesis. Treatment must be prompt and should consist of the rapid infusion of 25% salt-poor human serum albumin. This complication may be minimized by restricting the amount of fluid removed at any one time by paracentesis.

Within the past few years, extensive experience has accumulated attesting to the value of large doses of adrenal steroids in the treatment of the nephrotic syndrome. In general, two types of therapeutic programs are currently in use: (a) a short-term program designed to eliminate edema and (b) a more prolonged intermittent or continuous "maintainance" program. There is no doubt that many patients do respond to the administration of these agents by a diuresis. Treatment is often accompanied by considerable symptomatic improvement, and there is some evidence that these agents may favorably affect the ultimate outcome of the disease in children.

The use of large doses of these hormones poses several problems related to the diet of such patients. There is a marked tendency for adrenal steroids to produce sodium retention and hypertension; the latter effect is partly dependent upon salt retention but not completely so. Sodium restriction is therefore very desirable. Often because of the increased well-being of patients receiving steroids, sodium restriction can be more effectively carried out without compromising appetite. Another risk of steroid therapy is the production of potassium depletion due to the direct influence of these hormones upon the renal tubular secretion of potassium. If sodium restriction is carried out effectively, the risk of producing potassium depletion is small. However, supplemental oral potassium chloride should be provided as an additional precautionary measure. Serial study of the serum potassium and total CO_2 content should be carried out in order to detect potassium depletion.

RENAL TUBULAR DISORDERS

Within the past two decades, the existence of a new set of diseases of the kidney has been uncovered and studied. These disorders differ conceptually from those already discussed in that they represent highly selective biochemical defects of tubular function. In general, such defects are congenital and are frequently hereditary.

The incidence of these congenital renal tubular disorders is generally regarded as quite low. However, it is highly probable that diligent application of existing chemical technics will uncover a great many more cases.

Several of the most clearly characterized of these defects will be considered in this section, and the dietary therapy will be discussed. In contrast to the entirely supportive therapy of the diseases discussed in previous sections, treatment of many of these disorders is usually very rewarding although it cannot be completely definitive in the sense that the primary defect is corrected.

Renal Glycosuria (38): In many ways renal glycosuria provides the best example of the type of defect discussed in this section. This disease is a benign, often inheritable disorder in which the primary defect is one limiting the rate at which glucose can be reabsorbed from the glomerular filtrate by the proximal tubule ("low renal threshold"). Hence, although the blood sugar is normal, the tubules are unable to reabsorb all of the glucose being filtered, and glycosuria results. All other tests of kidney function are entirely normal, emphasizing the discrete nature of the defect. No treatment is indicated, as the loss of calories is generally small. Patients with this disorder should be informed as to the nature of their disease in order to prevent their being diagnosed as diabetics and receiving inappropriate insulin therapy.

Nephrogenic Diabetes Insipidus (39, 40): This disease, also known as "pitressin-resistant diabetes insipidus," represents a congenital inability of the renal tubules to respond to endogenous or exogenous antidiuretic hormone. Urine flow is obligatorily large and urine concentration is consistently less than the plasma concentration (*i.e.*, specific gravity is less than 1.010). These large losses of water, if unreplaced, lead rapidly to dehydration associated with elevation of the serum sodium and chloride concentrations. The latter, in turn, are potent stimuli to thirst.

The disease has its onset at birth, and these infants (so-called "water babies") will consume astoundingly large quantities of formula, milk and water. If the disease is not recognized at such an early age the hypertonicity becomes chronic and dehydration is an ever-present threat to life. The chronic hypertonicity is thought to cause permanent damage to the immature central nervous system, the most obvious clinical manifestation being mental deficiency.

As in the case of renal glycosuria, nephrogenic diabetes insipidus is an isolated defect. No abnormalities are demonstrable in other parameters of renal function (GFR, reabsorption of glucose, phosphate and amino acids, or acidification mechanisms).

In most instances the disease is hereditary following a sex-linked pattern in which males (hemizygotes) are affected while females (heterozygotes) are "carriers" having only a mild concentrating defect.

Treatment involves the adequate provision of water at all times. It is especially important to recognize the disease early in order to prevent the neurological sequellae of chronic hyperosmolarity. In infants, water should be offered frequently; in older patients, thirst is an accurate guide to water needs. Under no circumstances should fluid be restricted, and special precautions should be taken to insure adequate intake (orally or parenterally) during intercurrent illnesses. An added measure in treatment is the restriction of solute intake, since the final urine volume is markedly dependent upon the amount of solute (and water) which is not reabsorbed by the proximal tubule (see discussion of solute diuresis, above). The principal urinary solutes under nearly all circumstances are (a) urea derived from the intake of protein and (b) sodium chloride. Obviously, in an

infant or child, severe protein restriction, although it would limit the excretion of urea, would be detrimental to proper growth. On the other hand, most infant formulae contain over-generous amounts of sodium and chloride, and these may be restricted without harm unless, of course, large losses of these electrolytes are being incurred through sweating. Several formulae widely used in the feeding of normal infants are of the "low solute type," in which the total solute is considerably lower than in cows milk formulae. These are very helpful in the management of infants with nephrogenic diabetes insipidus.

Vitamin D Resistant Rickets (41): With the marked decline in the occurrence of Vitamin D deficiency — rickets resistant to vitamin D has become the most common form of rickets in the United States. Clinically and radiologically, this disease resembles ordinary deficiency rickets to a marked degree except that it is unresponsive to ordinary therapeutic doses of vitamin D. The disease begins in infancy and shows a relentless progress ending in severe residual deformities. As in the case of ordinary rickets, the immediate cause of the skeletal abnormalities is a decreased calcificability of the serum due to the low level of inorganic phosphorus. Studies of the renal function have revealed a defect in the reabsorption of phosphate from the glomerular filtrate. The prevailing opinion is that this defect involves the intrinsic mechanism for phosphate transport. However, the possible role of secondary hyperparathyroidism incident to a decreased absorption of calcium from the gastrointestinal tract cannot be completely excluded.

Vitamin D resistant rickets is nearly always hereditary, following a sex-linked dominant pattern in which males (hemizygotes) are affected with rachitic lesions and hypophosphatemia, while females (heterozygotes) have minimal or no skeletal disease but do "carry" the hypophosphatemic trait and the renal abnormality.

Treatment of the disease involves administration of pharmacologic doses of vitamin D (generally from 100,000 I.U. up to as much as 1,000,000 I.U. per day). The mechanism whereby these massive amounts of vitamin D effect a cure of the rachitic lesions is particularly obscure. There is little doubt, however, that careful management of such patients can do much to prevent serious deformities. Such large doses of vitamin D do carry the distinct risk of hypervitaminosis D with its attendant sequelae of hypercalcemia, nephrocalcinosis and permanent renal damage. Such complications must be carefully guarded against through serial study of the urinary calcium (Sulkowitch test) and of the serum calcium and blood urea nitrogen. Hypercalcemia, hypercalcuria or elevation of urea-nitrogen demand immediate withdrawal of vitamin D even at the risk of recurrence of the active rachitic process. Therapy should be resumed when normal values for the above parameters are again achieved (generally 1 to 3 weeks).

Recently the possibility of adding inorganic phosphate to the diet (1.0 to 1.5 gm of P per day) has been suggested as an additional measure (42). Preliminary studies with this measure combined with vitamin D have been encourag-

ing, particularly since the dosage of vitamin D can be reduced without reactivation of rickets. Further studies, however, are desirable before this therapy can be recommended as a routine measure.

Renal Tubular Acidosis (38): Under this heading are included several distinct clinical syndromes all having the common feature of a metabolic acidosis of the hyperchloremic type. Clinically, the picture varies from a self-limited disturbance in infants (Lightwood's syndrome) to a more permanent form of the disorder in infants and children, as well as a form which has its onset first in adult life. In some forms of the disease an hereditary factor is clearly evident; in others, the disease is clearly acquired.

Lightwood's syndrome (43), although prevalent in England, is rare in this country. Most infant cases in this country present a more permanent form of the disorder. Clinically, the disease in infants and children is characterized by weakness, anorexia, vomiting, constipation, poor growth and undernutrition. Polyuria and polydipsia (excessive thirst) are frequently encountered. In adults constitutional symptoms similar to those of affected children occur. Metabolic bone disease resembling rickets (in children) or osteomalacia (in adults) develops, although the rickets in these children is rarely clinically severe because of the general limitation of growth. Osteomalacia in adults is characterized by generalized demineralization and/or pseudofractures; bone pain may occur in such patients. In both adults and children, nephrocalcinosis and/or renal calculi may develop (21).

Biochemically, the cardinal abnormality is a chronic metabolic acidosis; the nature of the acidosis is fundamentally different from that encountered in acute or chronic renal failure. In renal tubular acidosis the fall in serum bicarbonate is nearly reciprocal with a rise in serum chloride ("hyperchloremic acidosis"), whereas in real failure there is an accumulation of acidic end-products (phosphate and sulfate) of metabolism.

In spite of the systemic acidosis the urine is generally alkaline, neutral, or only weakly acid, and contains appreciable amounts of bicarbonate in association with sodium and potassium, but little titratable acid or ammonia. Loading with ammonium chloride exaggerates the acidosis because the kidney is unable to increase the excretion of hydrogen ions either as titratable acid ammonium ion. All these observations suggest that there is a defect in the acidification mechanisms. Hence, in the absence of significant hydrogen ion secretion by the tubules, bicarbonate reabsorption and excretion of titratable acid and ammonium are diminished. With defective reabsorption of bicarbonate, the sodium which is reabsorbed occurs either with chloride or as the result of exchange with potassium. These features explain the hyperchloremia as well as the potassium losses.

There is disagreement as to the exact defect in the acidification mechanism. It has been assumed that there is a deficiency of carbonic anhydrase in the tubular cells, since the picture of renal tubular acidosis is quite similar to that occurring after the administration of an inhibitor of carbonic anhydrase (Diamox). In this

view, the failure of hydration of carbon dioxide to form carbonic acid, the latter being the source of hydrogen ions in the urine, is the defect in renal tubular acidosis. On the other hand, it is now clear that patients with renal tubular acidosis can under some circumstances secrete hydrogen ions, and administration of carbonic anhydrase inhibitors will bring about a discernible effect. Both of these observations suggest that carbonic anhydrase deficiency is not primarily at fault. An alternate suggestion is that the primary defect is one which limits the secretion of hydrogen ions against a steep gradient. This implies that the minimal pH of the urine of such patients is higher than the normal urinary pH of 4.5.

Nephrocalcinosis and renal calculi are generally thought to be the consequence of the increased calcium excretion characteristic of this condition. There is also a diminution of citrate excretion by the kidney, contributing to precipitation of calcium due to failure to form soluble calcium citrate complexes. The loss of calcium through the urine also contributes to the development of bone disease in renal tubular acidosis. One hypothesis (21) holds that this loss of calcium leads to secondary hyperparathyroidism (through transient hypocalcemia) and that this in turn leads to an accelerated excretion of phosphate. The end result is hypophosphatemia associated with normal or slightly low levels of serum calcium. Thus the calcifying ability of the serum is reduced and rickets (or osteomalacia) results.

The cause of the polyuria has not been completely elucidated. It may be due to an increased solute excretion, or to the development of potassium depletion, or it may represent another independent tubular defect akin to that occurring in nephrogenic diabetes insipidus. Some mild reduction in glomerular filtration rate is usual in renal tubular acidosis but this is not associated with azotemia or with any of the biochemical abnormalities.

Treatment of renal tubular acidosis is often dramatic. Although the primary defect in acidification mechanisms cannot be corrected, the acidosis can be attacked through providing exogenous alkalinizing salts orally. For this purpose Shohls mixture* has been widely used, the alkali being in the form of sodium citrate, which is metabolized to sodium bicarbonate. Adequacy of therapy should be assessed by frequent serial study of the serum electrolytes and total carbon dioxide content. Successful therapy will be accompanied chemically by a rise of total CO_2 to normal, and clinically by marked improvement in appetite, linear growth, weight gain and general well-being. During treatment the nutritional problem involves the provision of a completely adequate diet, preferably high in protein, in order to provide for optimal replacement of previously incurred nutritive deficits as well as to permit adequate growth. Since potassium wasting forms a prominent part of the picture in some patients, it is important

*Shohls mixture: 98 gm. of sodium citrate, 140 gm. of citric acid, water to make 1 liter. This mixture provides 1 mEq of Na per ml. The usual starting dose for an infant or young child is 30 to 45 ml/d in multiple divided doses. Subsequent modifications of dose should be based upon serial chemical examination of the serum.

to modify the therapy to provide supplemental potassium (potassium citrate) to avoid serious potassium depletion and alkalosis.

In any system of therapy for renal tubular acidosis, attack upon the acidosis must be the primary consideration. With successful correction of the acidosis, healing of the bone disease is generally a simple matter involving the provision of modest therapeutic doses of vitamin D (5,000 to 10,000 I.U./d). If acidosis is not corrected, the administration of large, even massive doses of vitamin D may not be successful. Supplemental vitamin D at the levels indicated above should be given along with alkali, since the growth spurt incident to correction of the acidosis may cause an exacerbation of rickets.

Fanconi Syndrome (44): This syndrome is characterized chiefly by the following abnormalities: (a) generalized renal aminoaciduria, (b) renal glycosuria (c) renal hypophosphatemia, which is often associated with rickets, (d) a renal tubular acidosis. The Fanconi syndrome may occur in several clinical settings. The disease may appear in infancy and in this age group it is associated with extensive deposits of cystine in various tissues (cystinosis). This form of the disease is frequently hereditary, behaving as a recessive trait, and its prognosis is grave. Another form of the disease in which cystinosis does not occur may be met either in children or in adults. Within the last few years there has been an increasing recognition that many if not all of these latter cases are acquired either as the result of a heavy metal poisoning (such as lead) or as a renal complication of other diseases (multiple myeloma, Wilson's disease).

Biochemically, many of the abnormalities of the Fanconi syndrome reflect failure of several tubular transport mechanisms. The prevailing view is that the syndrome is the result of multiple tubular defects. Hence, glycosuria, aminoaciduria and hyperphosphaturia all represent failure of proximal tubular functions. In fact, a morphologic abnormality has been described in the proximal tubule of patients with the Fanconi syndrome, which consists of a narrowing of the initial part of the tubule (swan-neck anomaly). In addition to these abnormalities of the proximal tubule, there is most probably a defect in the distal acidification mechanism. Finally, there is a suggestion that some patients may have a water reabsorptive defect, although this has not been evaluated.

The nature of disturbance in cystine metabolism in the infantile form of the disease is completely unknown. The effect of this disturbance, however, is a deposition of this amino acid (presumably because of its poor solubility) in the liver, spleen and other parts of the reticuloendothelial system as well as in the cornea of the eye and in the kidney. Cystinosis can, in fact, be diagnosed by slit-lamp examination of the eye or by examination of bone marrow aspirate for the characteristic cystine crystals.

Deposition of cystine in the kidney is thought to be responsible for the eventual renal failure (both tubular and glomerular) which characteristically occurs late in the course of the infantile form.

Hypophosphatemia plays an important role in the pathogenesis of rickets. Low serum phosphorus results from the hyperphosphaturia caused by the diminished tubular transport, although deficient calcium and phosphorus absorption from the gastrointestinal tract has also been demonstrated.

Treatment of the Fanconi syndrome should proceed along the lines already outlined in connection with renal tubular acidosis. It should be mentioned that massive doses of vitamin D have been claimed to improve many of the biochemical abnormalities of the Fanconi syndrome. However, it is not at all clear whether these effects are not simply due to a decrease in GFR secondary to vitamin D poisoning. Until satisfactory data are available on this point, this type of potentially dangerous therapy cannot be recommended.

Although the magnitude of the aminoaciduria is such as not to be important from the point of view of total nitrogen metabolism, it should be emphasized that specific amino acid deficiencies may very well exist. For this reason, adequate intake of protein of high biological quality is indicated.

POTASSIUM DEPLETION NEPHROPATHY

Thus far in this review we have been concerned mainly with the effects of renal disease upon metabolism and nutrition. There is, however, another side of the coin — namely, the effect of various nutritive deficiencies upon the structure and function of the kidney. Although there is a large body of evidence dealing with such effects, these findings have not as yet been shown clearly relevant to human nutrition or to clinical renal disease. However, there is one condition, that of potassium deficiency, which has important effects upon renal structure and function in patients and therefore deserves discussion.

Experimental Animals: It has long been recognized that dietary restriction of potassium in experimental animals, particularly the rat, is associated with marked pathologic changes in the renal tubules. Detailed study of these lesions in the rat has revealed two general types of change (45). The most consistent lesion is one confined to the collecting ducts of the nephron, the changes being predominantly a hyperplasia of both epithelial cells and intercalated cells. The latter are dark-staining cells which in the normal kidney are sparsely distributed in the more distal portions of the nephron; their function is unknown. In addition, colloid droplet formation within the cells of the collecting duct has also been seen. These lesions of the collecting duct are a consistent feature of potassium depletion in the rat and occur in virtually every nephron of the kidney. The other lesion of potassium depletion is a hyperplastic, degenerative one which involves the proximal tubule; this lesion shows considerable variation from nephron to nephron.

Functional studies of the kidneys of potassium-depleted rats are rather limited. One important derangement, however, has been described — an inability of such animals to produce a concentrated urine (46). Correlative structural and functional analysis of this defect has clearly indicated that the defect involves the

terminal concentrating mechanism which resides in the collecting duct. This location corresponds to the site of the maximal lesion of potassium depletion. It has been suggested that perhaps the lesion somehow interferes with the passive diffusion of water from the collecting duct back into the hypertonic medullary interstitium.

Human Potassium Depletion: A variety of clinical disorders may be associated with significant deficits of body potassium. These include chronic diarrhea, primary aldosteronism, various malabsorption syndromes, overuse of laxatives for constipation, ureterosigmoidastomy, (transplantation of ureters to colon) pyloric stenosis with vomiting, and others. Lesions of the renal tubules have been described in a number of these diseases, but only recently has the common denominator of potassium deficiency been noticed.

In human potassium depletion, the nature of the renal lesions differs somewhat from those of experimental studies in that they are vacuolar and degenerative and affect predominantly the proximal tubule (47). Lesions in the collecting ducts have not been reported, but the search has not been completely adequate. Glomerular lesions and lesions of blood vessels are not a part of uncomplicated potassium depletion in humans or animals.

Human potassium depletion is similar to that seen in the rat in that the most consistent functional abnormality is a failure of the urine concentrating mechanism. In severe depletion, the maximal urinary concentration approaches isotonicity and is unaffected by exogenous vasopressin (ADH). These findings are consistent with the notion that potassium depletion interferes primarily with the final step in the concentrating mechanism.

Other functional abnormalities have also been described. Glomerular filtration rate is slightly to moderately reduced as is renal plasma flow. There is also some reduction in the tubular secretion of phenol red and paraaminohippurate (PAH).

Treatment of potassium depletion nephropathy should be aimed primarily at eradicating the cause of the loss as well as at restoring bodily deficits. It is important to realize that potassium deficits cannot be safely or effectively replaced in a day or two. Rather, supplemental potassium must be given either orally or parenterally for a period of four to eight days or even longer. Serial study of the serum potassium and total CO_2 content is a helpful guide in judging the adequacy of therapy.

The renal lesions of potassium depletion generally show a fairly rapid reversal with repletion of body stores. Functional studies also show improvement, although generally a longer period is required. Some recent experimental evidence suggests that potassium depletion may produce permanent renal changes. (48). This facet of the problem has not been adequately evaluated in patients.

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